Lichen sclerosus: incidence and risk of vulvar squamous cell carcinoma

Maaike C.G. Bleeker¹, Pascal J. Visser², Lucy I.H. Overbeek³, Marc van Beurden⁴, and Johannes Berkhof⁵

¹ Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands
² Faculty of Medicine, VU University, Amsterdam, The Netherlands
³ Foundation PALGA, the Dutch Pathology Registry, Houten, The Netherlands
⁴ Department of Gynecology, Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands
⁵ Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

Running title: Lichen sclerosus: incidence and vulvar cancer risk

Key words: Lichen sclerosus, vulvar squamous cell carcinoma, incidence, cancer risk

Corresponding author: Maaike C. G. Bleeker, MD, PhD
Department of Pathology
VU University Medical Center
PO Box 7057
1007 MB Amsterdam
mcg.bleeker@vumc.nl
Phone number: +31 20 4444023

Financial support: None
Conflict of interest:

JB received consultancy fees from Merck, GSK, and Roche.
All fees were collected by his employer.

Word count manuscript: 3578
Word count abstract: 250
Number of tables: 3
Number of figures: 2
Abstract

Background
The association between lichen sclerosus (LS) and vulvar squamous cell carcinoma (VSCC) has long been recognized, but large epidemiological studies are lacking.

Methods
Data of women diagnosed with vulvar pathology in the Netherlands were retrieved from the Dutch Pathology Registry. All vulvar pathology reports of this historical cohort were reviewed to construct a research database, including 3038 women with LS diagnosed between 1991 and 2011. The incidence rate of LS and the cumulative incidence of VSCC among women with LS were estimated.

Results
Between 1991 and 2011, the incidence rate of LS increased from 7.4 to 14.6 per 100,000 woman-years. The median age at time of LS diagnosis was 59.8 years and the cumulative VSCC incidence was 6.7%. The 10-year VSCC incidence in women with LS was associated with concurrent vulvar intraepithelial neoplasia (VIN) (18.8% in women with VIN and 2.8% in women without VIN) and age at time of LS diagnosis (5.9% in women of ≥70 years, 3% in women between 50 and 70 years and 1.8% in women < 50 years). The effects of presence of VIN and age remained significant in adjusted Cox regression analysis.

Conclusion
This historical cohort showed a nearly 100% increase in incidence of LS between 1991 and 2011. Concurrent VIN and age ≥70 at time of LS diagnosis are important risk factors for vulvar cancer development.

Impact
The incidence of LS is rising and special attention is needed in particular in women with concurrent VIN because of their high risk of cancer.
Introduction

The incidence rate of vulvar cancer is about 2.4 to 3.4 per 100,000 woman-years and has been rising by 20 to 55% during the past decades.\(^{(1-6)}\) In the Netherlands, the incidence rate of vulvar cancer increased from 2.2 in 1990 to 3.4 per 100,000 woman-years in 2014.\(^{(3)}\) Vulvar squamous cell carcinoma (VSCC) accounts for about 90% of all vulvar cancers.\(^{(4)}\) Although the etiology of VSCC is not yet fully understood, it is recognized to be heterogeneous. It has been estimated that at least 25% of VSCC can be attributed to infection with human papillomavirus (HPV) while other important risk factors include vulvar inflammatory conditions like lichen sclerosus (LS).\(^{(7, 8)}\) The rise in the absolute number of vulvar cancer cases has even been more pronounced due to aging of the population.

Attempts to reduce vulvar cancer should focus on adequate recognition and treatment of precursor lesions including LS. High-grade vulvar intra-epithelial neoplasia (VIN) is considered as the precursor lesion of VSCC and can be categorized into HPV-induced or usual VIN (uVIN) and HPV-independent or differentiated VIN (dVIN), the latter often being associated with LS. Compared to uVIN, dVIN is not commonly diagnosed as a solitary diagnosis, partly because the clinical presentation is less characteristic than uVIN. In addition, histopathological features overlap with features that can be seen in reactive disorders with atypia confined to the basal layers resulting in missed diagnoses of dVIN.\(^{(9)}\) Another possible explanation for the fact that uVIN is more commonly diagnosed than dVIN is that the interval between uVIN and HPV-induced VSCC is thought to be much longer than the interval between dVIN and HPV-independent VSCC.\(^{(10, 11)}\) It has been conjectured that dVIN can develop from LS and that the presence of both strongly increases the cancer risk. A supportive observation is that both dVIN and LS are observed adjacent to VSCC in 25 to 65% of the cancer cases.\(^{(12-15)}\) Although the association between LS and VSCC has long been recognized, literature on the incidence of LS is lacking and studies on VSCC risk in women with LS are scant. Our aim was to estimate the incidence of LS and VSCC risk in LS women. Vulvar pathology data were retrieved from the Dutch Pathology Registry to identify an historical cohort of women including 3038 women diagnosed with LS between 1991 and 2011 in the Netherlands.
Material and Methods

Study design, data collection and study population

For this study, women diagnosed with LS between 1991 and 2011 were selected from a large historical cohort. All vulvar pathology reports of women with LS, VIN and/or VSCC diagnosed until June 2011 at one of the 23 pathology laboratories located in the provinces Noord-Holland and Flevoland were reviewed to construct a study database of this historical cohort. The provinces Noord-Holland and Flevoland are situated in the North-West of the Netherlands and comprise about 18% of the Dutch population. The pathology reports were extracted from PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands (in short the Dutch Pathology Registry). Every abstract transferred to PALGA contains encrypted patient identification data, the conclusion of the pathology report (free text), and a coding system, based on standard pathology terminology, including at least codes for topography (1), type of material (2) and diagnosis (3) that are automatically translated to SNOMED codes.(16) Only patients with vulvar LS, VIN and/or VSCC in one of the pathology laboratories within the provinces Noord-Holland and Flevoland were retrieved from PALGA and evaluated for eligibility (see supplementary table for specified search terms). Of these patients, pathology reports of the vulvar region (including the labia majora, labia minora, clitoris and perianal region) were obtained and for each report the free text of the conclusion was reviewed to categorize the diagnosis correctly. A total of 16,237 pathology reports of 5697 women were reviewed to categorize women with LS, VIN and VSCC. Since PALGA reached nationwide coverage in 1991, only women with LS diagnosed thereafter were selected for this study. Diagnoses of LS and possible LS were both categorized as LS. Possible LS included cases with interface dermatitis that could fit with an early phase of LS. Women with LS were excluded from the analyses when a history with VSCC was established. It should be noted that a history of VSCC is difficult to establish because LS often remains undiagnosed for a period of time. Therefore, a practical definition of history of VSCC was used, namely that the date at time of the first histological diagnosis of VSCC was at least 3 months earlier than the date at time of the first histological diagnosis of LS.

Statistical analysis
Incidence of LS. The crude incidence of LS was calculated from the number of women diagnosed with LS and the total number of woman-years in Noord-Holland/Flevoland (as available at tables of Statistics Netherlands).\(^{(17)}\) To calculate the incidence of LS by age, age-specific strata of 5 years were used (0-4 years, 5-9 years etc.). To evaluate the incidence over time, the calendar years were stratified into the periods 1991-1995, 1996-2000, 2001-2005 and 2006-2011. The European Standard Population for women (2013) was used to calculate the European Standardized Rate (ESR).

Risk of VSCC in women with LS. The incidence rate of VSCC per 100,000 woman-years at risk was calculated among women with LS. The Kaplan-Meier method was used to adjust for censoring. The begin date was defined as the date of the first histological diagnosis of LS and the end date was defined as the date of VSCC diagnosis. For women that did not develop VSCC, the end date was set equal to the earliest date of either the expected date of death at time of the last pathology report or the date of data extraction from the PALGA database (i.e. June 22\(^{nd}\), 2011). The expected date of death was based on national age dependent life expectancy tables of Statistics Netherlands at time of the last pathology report.\(^{(17)}\) When the interval between the diagnoses of LS and VSCC was shorter than 3 months, VSCC was assumed to be prevalent at time of diagnosis LS and these women were excluded in the VSCC risk calculations. Kaplan-Meier analyses were repeated setting this threshold at 6 months. Statified Kaplan-Meier analyses were performed to examine the effect of VIN at baseline (either VIN present at baseline or VIN not present at baseline) and for age-groups at first LS diagnosis (less than 50 years, 50 to 70 years or 70 years or older). Adjusted Cox regression analyses were performed to analyze independency of risk factors. Median age in different strata were compared by Mann-Whitney tests. The levels of statistical significance were set at 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, Illinois, USA).
Results

Incidence of LS

Between 1991 and 2011, 3038 women were diagnosed with histology proven LS within the provinces Noord-Holland/Flevoland in the Netherlands. The median age at first LS diagnosis was 59.8 years (range 1.6 – 95.4 years). Over time, the median age of LS diagnosis remained stable, respectively 60.9, 59.3, 59.3 and 59.9 years in the calendar periods 1991 - 1995, 1996 - 2001, 2001 - 2005 and 2006 - 2011.

The crude incidence rates and ESRs for LS are presented in Table 1. Between 1991 and 2011, the incidence rate of LS was 10.4 per 100,000 woman-years with the highest incidence rate of 28.6 per 100,000 woman-years achieved between 65-69 years of age. From 1991 to 2011, the incidence rate of LS diagnoses increased from 7.4 to 14.6 per 100,000 woman-years. The ESR showed a similar trend. Between 1991 and 2011, the ESR was 11.9 per 100,000 woman-years: 8.8 in 1991 - 1995, 9.5 in 1996 – 2000, 11.5 in 2001 – 2005 and 16.0 in 2006 – 2011.

Incidence of VSCC in women with LS

To assess the incidence rate of VSCC in women with LS, 163 women with LS were excluded because of prevalent VSCC (i.e. the interval to VSCC was less than 3 months), leaving 2875 women and a total of 22088.9 woman-years available for analyses. In total 75 (2.6 %) women developed incident VSCC at a median time of 3.3 years (range 0.27 – 18.4 years) after the LS diagnosis. The incidence rate of VSCC was 339.9 per 100,000 woman-years of LS.

The cumulative incidence of VSCC in women with LS is presented in Figures 1 and 2. Kaplan-Meier analyses showed a cumulative incidence of VSCC in women with LS of 2.1% (95% CI 1.5%-2.7%), 3.3% (95% CI 2.5%-4.1%), 4.1% (95% CI 3.2%-5.1%) and 6.7% (95% CI 4.0%-9.4%) after 5, 10, 15 and 20 years of follow-up, respectively (Figure 1).

When the threshold for the interval between LS and VSCC was set to 6 months for incident VSCC, results were very similar, i.e. 71/2875 (2.5%) developed incident VSCC. Similarly, Kaplan-Meier analyses revealed a cumulative incidence of VSCC in women with LS of 6.6% after 20 years of follow-up.
The 10-year cumulative incidence of VSCC in women with LS was significantly higher in LS women who had concurrent VIN at baseline compared to women without VIN at baseline (18.8%; 95% CI 9.2%-28.4% and 2.8%; 95% CI 2.0%-3.6%, respectively, log rank p-value < 0.001, Figure 2A).

Considering the 75 women with LS that developed cancer, 39 women (52%) were ever diagnosed with VIN: 15 women had VIN at baseline, 5 women were diagnosed with VIN after the diagnoses of LS and before the diagnoses of VSCC, 15 women were diagnosed with VIN at the same time as the VSCC diagnoses and 4 women were diagnosed with VIN after the VSCC diagnoses.

The 10-year cumulative incidence of VSCC in LS women increased with age and was 5.9% (95% CI 3.5%-8.3%) among women aged 70 and beyond, 3% (95% CI 1.8%-3.0%) among women between 50 and 70, and 1.8% (95% CI 0.6%-3.0%) among women below the age of 50 (Figure 2B). Log-rank p-values were 0.001 and 0.009 when comparing age group >70 with age groups under 50 and between 50 and 70, respectively. For the comparison of age group under 50 and age between 50-70, the p-value was 0.319.

Cox regression analysis adjusted for presence of VIN at baseline, age at LS diagnosis and period at LS diagnosis (1991 – 1995, 1996 – 2000, 2001 – 2005 and 2006 – 2011) showed that both the presence of VIN at baseline and an age of 70 years were independent risk factors for VSCC risk (Table 2). The period of LS diagnosis was not associated with VSCC risk.

**LS women with and without VSCC**

The age at first LS diagnosis in women without VSCC (median 59.1 years, range 1.6 – 95.4) was lower than the age at first LS diagnosis in women with VSCC, including both prevalent and incident cases of VSCC (median 71.0 years, range 30.0 – 92.3, p < 0.001, Table 3) or including only women with incident VSCC (median 64.4 years, range 30.0 – 88.7 years, p = 0.004). As VSCC was not observed in women diagnosed with LS under the age of 30 years, analyses were repeated in women of 30 years or older (n = 2648) yielding comparable results.

Considering only LS women with VSCC, the age at first LS diagnosis was higher amongst women with prevalent VSCC (median 75.0 years, range 34.1 – 92.3) compared to women with incident VSCC (median 64.4 years, range 30.0 – 88.7 years, p = 0.001). Similarly, the age at VSCC was higher among LS women with prevalent VSCC (median 75.0 years, range 34.6 – 92.3 years) compared to women with incident VSCC (median 68.8 years, range 34.7 – 89.5 years, p = 0.001).
Discussion

In this historical cohort, an incidence rate of 10.4 LS cases per 100,000 woman-years was observed between 1991 and 2011. To our knowledge, literature on the incidence of LS in the general population is virtually absent. The best data to reflect our results are described in an LS review published in 1999 by Powell and Wojnarowska who refer to an unpublished study on the incidence of LS in a cohort of 17,000 women with long term follow-up.(18) They describe a positive relation between age and LS and observed an incidence rate of histology proven LS of 14 per 100,000 woman-years in women between the age of 50 to 59 years (the oldest age group for which were data available). We found a comparable incidence rate of LS, ranging from 11.7 to 24.4 LS cases per 100,000 woman-years between 50 and 59 years of age in the calendar period up to the year 2000 (thereby excluding our data in the calendar periods after the publication date of this review).

Studies on LS are further complicated as referred patients may be seen by various specialists including dermatologists, gynecologists, urologists, geriatrics and pediatricians. Estimates in hospital referrals range from 1 to 17 cases of LS per 1000 patients.(18-20) Studying the prevalence of LS in a general gynecology practice, 28 out of 1,675 (1.7%) women were diagnosed with LS at a mean age of 52.6 years of whom at least one third was asymptomatic.(20) Although most cases of LS present in the genital area (i.e. 85-98% of the cases) and in women (female to men ratio varies between ten to one and six to one),(18, 21) it should be noted that both extragenital and male LS cases were not included in our study.

From 1991 to 2011, the incidence rate of histology proven LS nearly doubled from 7.4 per 100,000 woman-years between 1991 and 1995 to 14.1 per 100,000 woman-years between 2006 and 2011. This striking increase might be explained by less hesitancy to visit the general practitioner and by an increased biopsy rate during the study period. Of note, patients with clinically diagnosed LS that were not biopsied were not included in our study. This could bias the results in particular in the lowest age groups, since clinicians are more reluctant to biopsy children suspected for LS, not only because of the physical burden of the biopsy procedure but also because of their low cancer risk. This might also affect the median age of LS in the whole study cohort although the median is considered a fairly robust measure of central tendency. A biopsy of a lesion suspected for LS is generally recommended, not only to rule out (pre) malignancy but also to differentiate LS from other vulvar dermatosis.(18, 22)
Another explanation for possible underestimation of the LS incidence could lie in the possibility that a histology proven LS might not have been coded as such by pathologists. Instead, codes like inflammation or reactive changes could have been used, resulting in missed cases of LS.

A 20-year VSCC incidence of 6.7% was observed in our historical cohort. An association between LS and VSCC has long been recognized. Carlson et al. reviewed the published literature and reported a pooled proportion of 4.5% (140/3093) VSCC arising in LS. When including only studies of more than 100 LS cases, a pooled proportion of 4.0% was estimated. In comparison, in our study the proportion of VSCC cases was 2.6% (75/2875). Most studies included in the review of Carlson were retrospective and case-series were often poorly defined. In our study, in all women the diagnosis of LS was histology proven. Moreover, women with LS in whom VSCC was diagnosed within 3 months after the LS diagnosis were excluded in the analyses as we believe that this group represents women with prevalent VSCC that visit a doctor primarily because of cancer and not for complaints of LS. In fact, in 163 of the 238 (68.5%) LS women with VSCC presented with prevalent VSCC. In this latter group, most likely, LS was present prior to VSCC but remained undiagnosed because of lack of serious symptoms and/or lack of patients’ need to visit a doctor. Compared to women with prevalent VSCC, the age at LS diagnosis was significant lower in women with incident VSCC. Similarly, the age at VSCC was significantly higher in women with prevalent VSCC compared to women with incident VSCC. To obtain more insight in the clinical relevance of prevalent versus incident VSCCs, further studies are needed, for instance on the association with FIGO stage at the time of VSCC diagnosis.

Of interest is the finding that LS women with concurrent VIN had a 10-year VSCC risk of 18% compared to 3% in LS women without VIN. Although the sequence of LS-VIN-VSCC could only be established in a minority of LS cases that developed VSCC, this does not necessarily mean that other patients did not progress via VIN. The role of VIN is further supported by the observation that 39 of the 75 women (52%) included in the cancer risk analyses were diagnosed with VIN as well. This proportion is likely to be a conservative estimate due to underreporting of VIN in pathology reports of VSCCs. Of note, studies in which VSCC cases were reviewed, reported dysplastic features in adjacent squamous areas in 77%(11), 72%(13), 31%(15) and 49%(12) of the cases. Differentiated VIN (dVIN), the type of VIN expected to be associated with LS, was uncommonly diagnosed in our database (less than 3% of the high-grade VIN diagnoses were diagnosed as dVIN, results not shown).
which is in agreement with the literature. A likely explanation of the low number of dVIN diagnosed is misclassification into lichen sclerosis, mild dysplasia, reactive changes or inflammatory dermatosis because of overlapping histological features. Van de Nieuwenhof et al., who studied LS cases that progressed to VSCC, found that 42% of the biopsies initially diagnosed as LS were reclassified as dVIN after revision. The variety in histopathological features in dVIN is diverse ranging from atrophic to verruciform variants. Positive p53 staining might be helpful to differentiate between reactive changes and dVIN but not all cases of dVIN show p53 positivity in neoplastic cells which is in line with findings observed in VSCCs. The paradox that dVIN is less commonly diagnosed than HPV related VIN while most of the VSCCs are HPV negative has been ascribed to underdiagnoses of dVIN but it has also been hypothesized that the interval between HPV negative dVIN and VSCC is much shorter than the interval between HPV induced VIN and VSCC, The latter hypothesis is supported by the finding that women diagnosed with HPV related VIN are much younger than women with dVIN. Despite these differences in clinical behavior between HPV negative and HPV positive carcinogenesis, HPV testing in vulvar neoplasia is not performed routinely in the Netherlands. In our historical cohort less than 10% of women with vulvar neoplasia were tested for HPV (results not shown). In these series, a considerable part of HPV negative cases were diagnosed with VIN without further specification into dVIN.

Risk factors for cancer development in women with LS remain largely unknown. Unknown clinical aspects include response to therapy (corticosteroids), genetic predisposition, immune status and smoking. Certain (epi)genetic events in LS might be involved in carcinogenesis but data in literature on this topic are lacking. To summarize, many aspects of HPV negative vulvar carcinogenesis, sequencing LS-VIN-VSCC, remain unclear because lack of structural studies. As long as clinicopathological characteristics are not able to stratify LS women at high or low risk for VSCC, it seems useful to control women with LS and monitor for alterations within areas affected by LS. Given the higher risk on VSCC, our results implicate that monitoring should be intensified in LS women with concurrent VIN or women at higher age.

Lack of attention for vulvar pathologies in elderly women might explain the decreased incidence of LS after the age of 80 years, as observed in our study. In a study of Leibovitz, who studied 96 women in an elderly nursing home at a mean age of 82 years, one-third of the women had vulvovaginal pathologies and 3% had LS. Therefore, special attention in vulvar care might be needed in elderly
women, especially when taking into account that the incidence of VSCC is considerably higher in women diagnosed with vulvar LS after an age of 70 years compared to women diagnosed with LS at younger age groups. A higher risk of VSCC in elderly age groups was also found by others.(23) To date, this study on VSCC risk in women with LS is the largest study including more than three thousand women with histology proven LS. Another strength of our study is that our results are based on a population of LS women that likely represents the general female population. The Dutch Pathology Registry has nationwide coverage, meaning that all pathology reports are included in this database. Our constructed database covers about 18% of the female Dutch population. Moreover, this database reached nationwide coverage in 1991 enabling us to retrieve data over a 20-year period including LS women with long-term follow-up. Despite the long term period of this historical cohort study, it should be noted that the follow-up period in this study might be too short to draw conclusions considering the cancer risk in young women (ie women with LS diagnosed under the age group of 30 years). The advantage of the Dutch Pathology Registry is the possibility to re-evaluate the cancer risk in our historical cohort after another 10 or 20 years of follow-up.

In conclusion, this historical cohort study showed a doubling in LS incidence from 1991 to 2011. The 20-years VSCC risk in women with LS is 6.7% and special attention is needed in LS women with VIN as well as in women above the age of 70 years as these women have an increased risk for VSCC.
Reference List


(9) van de Nieuwenhof HP, Bulten J, Hollema H, Dommerholt RG, Massuger LF, van der Zee AG, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma. Mod Pathol 2011;24:297-305.


Table 1: Incidence rate of lichen sclerosus (LS) per 100,000 woman-years between 1991 and 2011

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>5-9</td>
<td>0.8</td>
<td>1.4</td>
<td>1.4</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>10-14</td>
<td>0.3</td>
<td>0.3</td>
<td>0.0</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>15-19</td>
<td>0.5</td>
<td>0.0</td>
<td>1.3</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>20-24</td>
<td>1.1</td>
<td>0.9</td>
<td>1.9</td>
<td>3.5</td>
<td>1.9</td>
</tr>
<tr>
<td>25-29</td>
<td>2.6</td>
<td>3.5</td>
<td>4.3</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>&lt; 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.2</td>
<td>1.6</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>30-34</td>
<td>3.4</td>
<td>4.5</td>
<td>5.5</td>
<td>5.5</td>
<td>4.7</td>
</tr>
<tr>
<td>35-39</td>
<td>5.2</td>
<td>4.6</td>
<td>4.5</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>40-44</td>
<td>7.2</td>
<td>5.5</td>
<td>6.0</td>
<td>9.8</td>
<td>7.3</td>
</tr>
<tr>
<td>45-49</td>
<td>8.9</td>
<td>9.0</td>
<td>9.3</td>
<td>11.0</td>
<td>9.7</td>
</tr>
<tr>
<td>30-49</td>
<td>6.0</td>
<td>5.8</td>
<td>6.2</td>
<td>8.5</td>
<td>6.7</td>
</tr>
<tr>
<td>50-54</td>
<td>11.7</td>
<td>12.2</td>
<td>18.7</td>
<td>26.3</td>
<td>18.4</td>
</tr>
<tr>
<td>55-59</td>
<td>17.4</td>
<td>24.4</td>
<td>24.4</td>
<td>34.0</td>
<td>26.5</td>
</tr>
<tr>
<td>60-64</td>
<td>18.5</td>
<td>19.4</td>
<td>23.4</td>
<td>41.4</td>
<td>28.1</td>
</tr>
<tr>
<td>65-69</td>
<td>20.2</td>
<td>21.7</td>
<td>28.2</td>
<td>40.4</td>
<td>28.6</td>
</tr>
<tr>
<td>70-74</td>
<td>20.7</td>
<td>23.6</td>
<td>29.3</td>
<td>34.2</td>
<td>27.2</td>
</tr>
<tr>
<td>75-79</td>
<td>21.1</td>
<td>24.8</td>
<td>23.2</td>
<td>34.9</td>
<td>26.5</td>
</tr>
<tr>
<td>80-84</td>
<td>17.5</td>
<td>17.1</td>
<td>25.1</td>
<td>33.0</td>
<td>24.1</td>
</tr>
<tr>
<td>85-89</td>
<td>12.2</td>
<td>5.1</td>
<td>19.6</td>
<td>23.9</td>
<td>16.2</td>
</tr>
<tr>
<td>90-94</td>
<td>9.2</td>
<td>10.5</td>
<td>9.6</td>
<td>5.4</td>
<td>8.3</td>
</tr>
<tr>
<td>95 +</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.8</td>
<td>2.5</td>
</tr>
<tr>
<td>≥ 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.4</td>
<td>19.0</td>
<td>23.4</td>
<td>33.4</td>
<td>24.4</td>
</tr>
<tr>
<td>All ages</td>
<td>7.4</td>
<td>8.1</td>
<td>10.1</td>
<td>14.6</td>
<td>10.4</td>
</tr>
<tr>
<td>crude incidence</td>
<td>8.8</td>
<td>9.5</td>
<td>11.5</td>
<td>16.0</td>
<td>11.9</td>
</tr>
</tbody>
</table>
Table 2: Prognostic factors for vulvar squamous cell carcinoma (VSCC) in women with lichen sclerosus (LS)

<table>
<thead>
<tr>
<th>Presence of VIN at baseline</th>
<th>Number</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>2786</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89</td>
<td>7.6</td>
<td>(4.3 – 13.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at LS diagnosis</th>
<th>Number</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>766</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 – 70 years</td>
<td>1431</td>
<td>1.4</td>
<td>(0.7 – 2.6)</td>
<td>0.306</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>678</td>
<td>2.9</td>
<td>(1.5 – 5.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Period at LS diagnosis</th>
<th>Number</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 - 1995</td>
<td>478</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996 - 2000</td>
<td>540</td>
<td>1.3</td>
<td>(0.7 – 2.6)</td>
<td>0.336</td>
</tr>
<tr>
<td>2001 - 2005</td>
<td>694</td>
<td>1.2</td>
<td>(0.6 – 2.5)</td>
<td>0.602</td>
</tr>
<tr>
<td>2006 - 2011</td>
<td>1163</td>
<td>1.4</td>
<td>(0.6 – 3.1)</td>
<td>0.396</td>
</tr>
</tbody>
</table>

Cox regression analysis was performed to calculate the adjusted hazard ratio (HR) and 95% confidence intervals (CI). Adjustments were made for all factors in the table and statistical significance is presented in bold.
Table 3: Age at lichen sclerosus (LS) and vulvar squamous cell carcinoma (VSCC) diagnosis

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Median</th>
<th>Range</th>
<th>Age at first VSCC diagnosis</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS</td>
<td>3038</td>
<td>59.8</td>
<td>1.6 – 95.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without VSCC</td>
<td>2800</td>
<td>59.1</td>
<td>1.6 – 95.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 years</td>
<td>2648</td>
<td>59.9</td>
<td>30.0 – 95.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with VSCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prevalent</td>
<td>238</td>
<td>71.0</td>
<td>30.0 – 92.3</td>
<td>73.3</td>
<td>34.6 – 92.3</td>
<td></td>
</tr>
<tr>
<td>incident</td>
<td>163</td>
<td>75.0</td>
<td>34.7 – 92.3</td>
<td>75.0</td>
<td>34.6 – 92.3</td>
<td></td>
</tr>
<tr>
<td>incident</td>
<td>75</td>
<td>64.4</td>
<td>30.0 – 88.7</td>
<td>68.8</td>
<td>34.7 – 89.5</td>
<td></td>
</tr>
</tbody>
</table>

Median age of women with LS without VSCC (59.1 or 59.9*) versus with VSCC (71.0), p < .001 or < .001*.
Median age of women with LS with prevalent VSCC (75.0) versus incident VSCC (64.4), p < .001.
Median age of women with LS without VSCC (59.1 or 59.9*) versus incident VSCC (64.4), p = .004 or p = .0029*.
Median age of women with incident VSCC (68.8) versus prevalent VSCC (75.0), p < .001.
*including only women of 30 years and older
Legends figures:

**Figure 1:** Cumulative incidence of vulvar squamous cell carcinoma (VSCC) in women with lichen sclerosus (LS)

**Figure 2:** Cumulative incidence of vulvar squamous cell carcinoma (VSCC) in women with lichen sclerosus (LS), stratified for the presence of vulvar intraepithelial neoplasia (VIN) at baseline (A) and stratified for age group at time of LS diagnosis (age in years) (B)
Lichen sclerosus: incidence and risk of vulvar squamous cell carcinoma


Cancer Epidemiol Biomarkers Prev Published OnlineFirst June 2, 2016.

Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-16-0019

Supplementary Material
Access the most recent supplemental material at:
http://cebp.aacrjournals.org/content/suppl/2016/06/02/1055-9965.EPI-16-0019.DC1

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.